Addressing Oxidative Stress in the Transition Cow and her Calf[1]

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Introduction

Dairy cattle can succumb to illnesses at any given time. However, the majority of diseases take place around to clusters: (1) the time around calving, commonly referred to as periparturient period, for metabolic and infectious diseases (e.g., ketosis, displaced abomasum, mastitis, metritis, etc.); and (2) the first few weeks of life, referred to as neonatal period, for diseases of calves (e.g., diarrhea or pneumonia). These periods of increased disease susceptibility are attributed to dysfunctional immune responses in these animals. Studies performed in the last decade clearly indicate that adult dairy cows experience oxidative stress (OS) around the time of calving (Castillo et al., 2003; 2005; 2006; Sordillo and Aitken, 2009; Abuelo et al., 2013, 2015). Also, some recent research has also documented that neonatal calves experience OS during the first few weeks of age (Gaal et al., 2006; Abuelo et al., 2014; Ranade et al., 2014). OS diminishes functional capabilities of immune cell populations and increases the animals' susceptibility to diseases (Sordillo and Aitken, 2009). In this presentation, the current knowledge regarding the impact of OS in these periods of increased disease incidence in dairy cattle populations.

Oxidative Stress vs. Oxidant Status

These terms have been used interchangeably in many instances. However, we now know that there is a clear difference between OS and oxidant status that should be considered. Oxidant status refers to the balance between the production of reactive oxygen/nitrogen species (ROS/RNS) and the total antioxidant capacity, whereas OS refers to the oxidative damage resulting from the imbalance between oxidants and antioxidants. OS includes oxidative modification of cellular macromolecules, cell death by apoptosis or necrosis, as well as structural tissue damage (Lykkesfeldt and Svendsen, 2007). It is expected that oxidative damage occurs as a result of shifts in the oxidant balance. Nevertheless, not all shifts in redox balance will result in OS, given that ROS/RNS are essential for many physiological processes and, therefore, changes in oxidant status might just reflect changes in redox signaling that are not associated with cell or tissue dysfunction.

This difference between OS and oxidant status also impacts the information that the different biomarkers provide. A review of the different methods available to measure OS or oxidant status is beyond the scope of this paper, and the readers are directed to

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previously published reviews (Palmieri and Sblendorio, 2007a, b; Celi, 2011a). However, it is important to understand whether the biomarker is an indicator of an oxidatively damaged molecule (e.g., isoprostanes, advanced oxidation protein products) or an indicator of the balance between pro- and antioxidants (e.g., Oxidant Status index (OSi); Abuelo et al. (2013))

Oxidative Stress in the Periparturient Period

Dairy cows go through dramatic physiological changes to prepare for the onset of lactation and peak milk production. In the peripartal cows, dry matter intake (DMI) decreases around parturition, whereas energy and calcium demands for lactation increase (Chapinal et al., 2012). In this situation, tissues consume more oxygen through normal cellular respiration during times of increased metabolic demand in order to provide the energy needed for the onset of lactation (Chapinal et al., 2012; Konvičná et al., 2015), resulting in energy deficit (ED). After calving, most cows undergo a period of ED, in which the energy demand for milk synthesis is not covered by feed intake. To meet the increased energy demands, cows mobilize body reserves predominantly from adipose tissue. Increased lipid mobilization as a consequence of ED may increase the generation ROS and RNS (Sordillo and Raphael, 2013; Celi and Gabai, 2015). An imbalance between both products coupled with the decreased intake of dietary antioxidants due to decreased overall feed intake can lead to a pro-oxidant shift in the redox balance that ultimately result in OS (Castillo et al., 2005; Dalle-Donne et al., 2005; Sordillo and Aitken, 2009). OS has been proposed as the nexus between the metabolic and immune systems of the cows during this stage (Sordillo and Mavangira, 2014; Abuelo et al., 2015).

Oxidative Stress and Periparturient Disease

Oxidative stress is a significant underlying factor to dysfunctional host immune and inflammatory responses that can increase the susceptibility of dairy cattle to a variety of health disorders, particularly during the transition period (Sordillo and Aitken, 2009). OS is known to diminish functional capabilities of immune cell populations and, therefore, increases the animals' susceptibility to infectious diseases during the periparturient period (Cemerski et al., 2003; Mehrotra et al., 2009; Abd Ellah et al., 2015). A more detailed description of the role of OS on periparturient cattle diseases is available elsewhere in these proceedings (Sordillo, 2019).

Owing to the role of OS in the pathophysiology of periparturient disease, biomarkers of OS and oxidant status have been proposed as potential predictors of disease (Celi, 2011b; Sordillo and Mavangira, 2014; Abuelo et al., 2015). Nevertheless, neither reference intervals nor cut-off points for OS biomarkers have yet been established to identify individual cows suffering from OS or to predict the likelihood of disease events or impairment of production outcomes at the herd level. Therefore, the application of these biomarkers in the field is still limited. Nevertheless, a recent study showed that biomarkers of oxidant status had a higher ability to predict fresh cow diseases at dry-off compared to commonly biomarkers of nutrient utilization such as nonesterified fatty acids, beta-hydroxybutyrate, calcium, etc. (Wisnieski et al., 2019). Thus, including biomarkers of OS in herd monitoring protocols has the potential for allowing earlier detection of cows/cohorts at risk and to better inform nutritional management strategies such as antioxidant supplementation.

Preventing Periparturient Disease with Antioxidant Supplementation

In the literature, there are several strategies that have been proposed and tested as a method to avoid the development or at least minimize the development of OS status during the transition period (Lykkesfeldt and Svendsen, 2007; Politis, 2012; Abuelo et al., 2015). However, it should be noted that antioxidant supplementation has shown inconsistent results on dairy cows' health and production. Whilst most studies reported an improvement in health status or productivity, some studies have also shown no effect or even detrimental effects. The review of all the antioxidant supplementation studies is beyond the scope of this article and the readers should consult some of the relevant review articles (Politis, 2012; Abuelo et al., 2015). Here, only the underlying principle of most of these strategies is described: increasing the animals' antioxidant capacity so that it is better equipped to counteract the increase in free-radical production.

To inhibit impaired biological function due to damage to macromolecules by ROS/RNS, living organisms have developed a complex antioxidant defense system. Endogenous antioxidants can be divided into three major groups: enzymatic antioxidants, nonenzymatic protein antioxidants, and nonenzymatic low-molecular-weight antioxidants (Miller et al., 1993). Of these, the nonenzymatic antioxidants are primarily responsible for the antioxidant capacity of plasma. For example, the lipid-soluble α-tocopherol (vitamin E) protects cell membranes from lipid peroxidation; ascorbic acid (vitamin C) and β-carotene are able to quench singlet oxygen and peroxyl radicals and enhance the antioxidative effect of α-tocopherol. Other vitamins, such as retinol (vitamin A), only show antioxidant activity *in vitro*, but not *in vivo* (Azzi et al., 2004). Nevertheless, the study by LeBlanc et al. (2004) demonstrated that in the last week prepartum, a 100 ng/mL increase in serum retinol was associated with a 60% decrease in the risk of early lactation clinical mastitis. In addition, the authors observed significant positive associations of peripartum serum concentrations among α-tocopherol, β-carotene, and retinol.

In general terms, vitamins and certain trace minerals, such as selenium (Se), have been proven to be effective in counteracting OS and the severity of several dairy cattle diseases such as mastitis or metritis both through a direct antioxidant effect and by enhancing the immune response (Abuelo et al., 2015). Most of the established nutritional requirements traditionally focus on deficiency situations and there is now evidence that supplementation slightly above these reported requirements can improve animal health status and performance (Abuelo et al., 2015), as well as the quality of the final product (Castillo et al., 2013). Nevertheless, some studies reported deleterious effects of excessive antioxidant supplementation, such as the increase of odds for mastitis due to the increased production of ROS (Bouwstra et al., 2010a; 2010b). Hitherto, the level to which antioxidant supplementation stops being beneficial and starts to be associated with harmful consequences remains unknown. Hence, antioxidant supplementation strategies must be implemented only to levels slightly above current recommendations unless strong scientific evidence is available to support its inclusion at a higher rate. The establishment of critical thresholds of OS biomarkers in periparturient dairy cattle will help inform more accurate antioxidant supplementation strategies.

Oxidative Stress in the Neonatal Period

The neonatal period of dairy calves is another time of increased disease susceptibility. Average neonatal morbidity and mortality rates are consistently reported above benchmarks worldwide, making high calf loss rates an international welfare problem (Mellor and Stafford, 2004; Mee, 2013). In the US dairy industry, pre-weaning morbidity and mortality rates are approximately 33 and 7-11%, respectively (NAHMS, 2014). As newborn calves adapt to the extra-uterine life, OS may contribute to increased disease susceptibility. However, redox biology also plays an important role in several physiological processes at this stage (Mutinati et al., 2014). As mentioned above for the periparturient period, it is the balance between the generation of ROS and the antioxidative capabilities of the animal that influence the development of OS and the subsequent development of systemic and localized dysfunctions. In the next sections we discuss different stages that lead to increased oxidant status during the neonatal period, as well as the knowledge available linking OS in calves with neonatal diseases and different prevention strategies.

In-Utero Conditions

The negative impact of metabolic stress on the immune function, health, and production of dairy cattle during this period is well established (Kehrli et al., 1989; Sordillo and Aitken, 2009). Metabolic stress starts several weeks before calving (Grummer, 1993; Sordillo and Raphael, 2013) and therefore can potentially affect the fetus. There is evidence in other non-ruminant species that maternal hypothalamic-pituitary-adrenal axis stress during gestation influences fetal development and exerts carryover effects on the offspring (McMillen and Robinson, 2005; Merlot et al., 2008). Studies in humans and murine models demonstrated that suboptimal intrauterine conditions during critical periods of development lead to changes in tissue structure and function (Fowden et al., 2006), that may have long-term consequences on the offspring's physiology and disease susceptibility (McMillen and Robinson, 2005; Merlot et al., 2008). Studies in ruminants have also demonstrated that exposure to heat stress and restricted or excessive energy intake during late gestation affects the immune and metabolic function of the offspring (Gao et al., 2012; Tao et al., 2012; Osorio et al., 2013; Tao et al., 2014; Yates et al., 2018). Moreover, Monteiro et al. (2016) demonstrated that the detrimental effects of in-utero exposure to heat stress on milk yield and reproductive performance extend to at least the first lactation of offspring. Thus, prenatal conditions have the potential of significantly impacting the productivity and health status of replacement heifers.

A recent study by Ling et al. (2018) compared the metabolic status and lipopolysaccharide (LPS)-induced whole blood TNFα release between calves born to cows that experienced different degrees of maternal metabolic stress during the last month of pregnancy. They found that calves born to cows with higher NEFA or OSi showed lower bodyweight at birth and throughout the study, whilst no association between any of the maternal groups and average daily gain at 4 weeks of age was identified. Serum concentrations of ROS were higher in calves exposed to higher maternal NEFA concentrations or OSi when compared to calves born to cows with lower values of these biomarkers. Calves exposed to high maternal OS also had higher circulating concentrations of haptoglobin and TNFα, indicating greater basal inflammatory responses when compared to calves born to cows with a lower OSi. In contrast, LPS-induced inflammatory responses were less robust in calves exposed to higher maternal biomarkers of inflammation or OS, suggesting compromised immune responses to microbial agonists. Collectively, their results suggest that prenatal exposure to maternal parameters of metabolic stress (altered nutrient utilization, dysregulated inflammation, and OS) may adversely impact some metabolic and inflammatory responses of the offspring that could influence disease susceptibility. Hence, the metabolic stress experienced by periparturient cows not only predisposes the cows to transition cow disorders but also has carry-over effects on its offspring. However, further studies are still required to determine the clinical impact of these carry-over effects in the health and growth of the offspring to allow the development of adequate management practices. Nevertheless, some studies supplementing late-gestation cows with limiting amino acids or trace minerals have showed promising results in improving the immunometabolism of newborn calves (Jacometo et al., 2016), although the impact of such interventions in reducing calf morbidity and mortality rates remains unexplored.

The abovementioned study focused on the last month of pregnancy because this is when the time when maternal periparturient immune dysfunction starts and the period with the fastest proliferation of immune cells in the bovine fetus. Nevertheless, it still remains unexplored whether other critical windows of maternal metabolic stress exposure that can compromise the development of the fetal immune response exist. Similarly, it still needs to be elucidated in dairy cattle if OS is a key factor in adverse pregnancy outcomes as it has been reported in humans (Cuffe et al., 2017; Sultana et al., 2017).

The Oxidative Challenge of Birth

After birth, mammals are exposed for the first time to an oxygen rich environment once they start to breathe and this results in an increase in the production of ROS (Saugstad, 2003; Wiedemann et al., 2003). In humans, a brief oxygen exposure at birth induced a relatively long-lasting OS status (Saugstad, 2003). Hence, birth-associated OS might have relevant impacts in calves' cell growth, development, and death. Similar findings were identified in calves. Gaal et al. (2006) found that the concentration of ROS in calves' blood was 30% higher than in their dams shortly after birth and before colostrum ingestion. Given that pulmonary respiration and exposure to oxygen following birth are essential to maintain life, interventions to counteract birth-associated OS should focus on increasing the calves' pool of antioxidants.

Oxidant status during the pre-weaning period

A few studies have investigated the shifts in oxidant status during the first weeks of life in dairy calves. Gaal et al. (2006) noted that the blood concentration of free radicals was lower than day 1 at days 3 and 7 of age but increased again at 2 and 3 weeks of age. Conversely, other studies did not find and age effect in the concentration of ROS (Abuelo et al., 2014; Ranade et al., 2014). However, these studies used different biomarkers to assess pro-oxidant status. Nevertheless, Abuelo et al. (2014) indicated lower antioxidant status of newborn calves while they were being fed milk replacer but these changes in antioxidant potential were not found in the study by Ranade et al. (2014) where calves were fed whole milk until weaning. Milk replacers were found to have a low antioxidant capacity (Soberon et al., 2012). Thus, calves fed milk replacer might benefit from additional antioxidant supplementation.

Of particular interest is to note that biomarkers of oxidant status in calves were higher than those of periparturient cattle (Gaal et al., 2006; Abuelo et al., 2014). Hence, OS might play a very significant role in neonatal calf health. Indeed, OS is known to play a key role in the initiation and maintenance of important calf diseases such as diarrhea or pneumonia (Ranjan et al., 2006; Lykkesfeldt and Svendsen, 2007). A detailed description of the role of OS in disorders of ruminants is beyond the scope of this paper and readers are encouraged to consult the review by Celi (2011b) for this.

Another important factor to consider is the role of OS in the modulation of the immune response of newborn calves. There is currently solid evidence from *in vitro* and human studies proving that OS significantly impacts T lymphocyte functions (Figure 1): (1) polarization of T cell differentiation toward a Th2 phenotype (King et al., 2006), (2) T cell hyporesponsiveness to stimulation-induced activation (Cemerski et al., 2003), and (3) induction of apoptosis and inhibition of proliferation in T cells (Bhattacharyya et al., 2007; Thoren et al., 2007; Kasic et al., 2011).

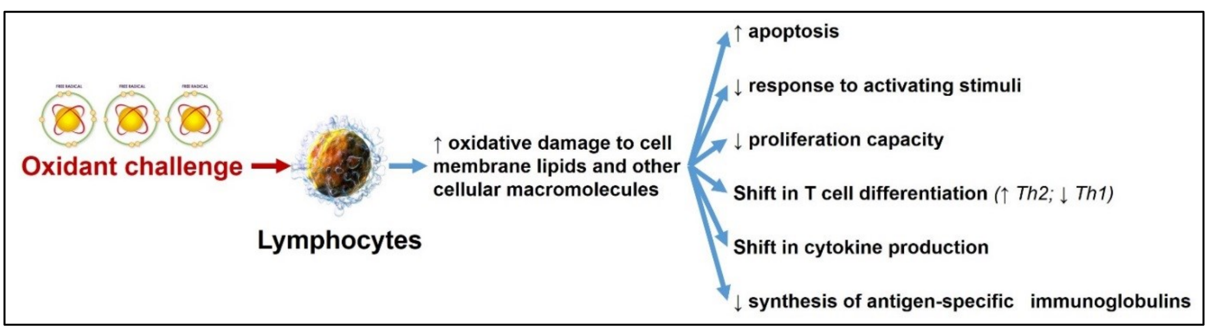

Figure 1: Schematic representation of the effect of prolonged exposure to ROS on human lymphocytes.

These functions of lymphocytes are essential for generating an adequate memory response and ensuring vaccination success. The degree of oxidant status experienced in newborn calves is also associated with differences in their profile of plasma circulating cytokines (Figure 2) and gene expression of key cytokines in PMBCs (Figure 3) (Abuelo and Sordillo, 2018).

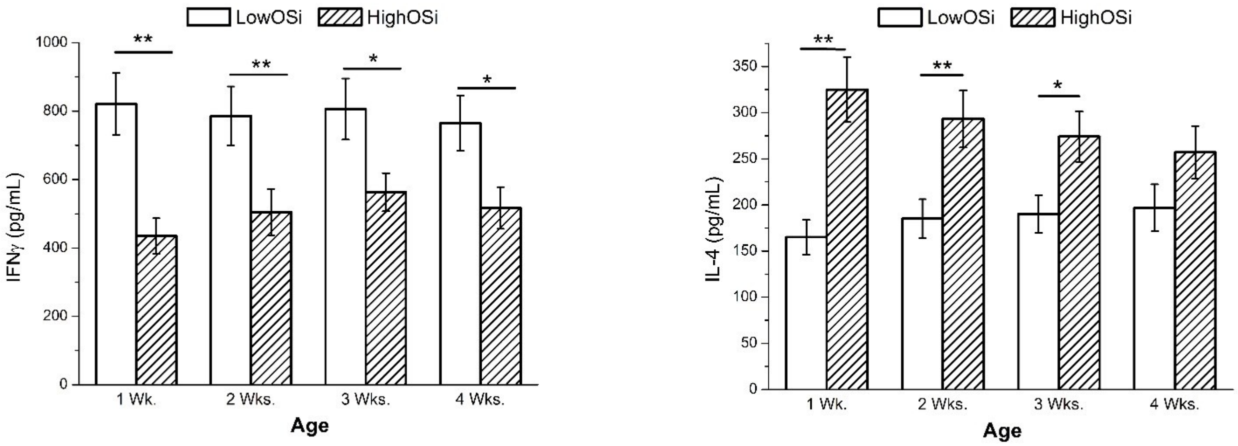

Figure 2. Plasma concentration of IFN-γ (left) and IL-4 (right) according to the calves' oxidant status throughout the first month of life. The oxidant status index (OSi) was monitored in sera of 12 healthy calves from the same farm by weekly blood sampling during their first month of life. Averages of OSi were calculated, and the calves were classified according to these values (Low OSi group = six lowest average OSi values). * $P < 0.05$, ** $P < 0.01$.

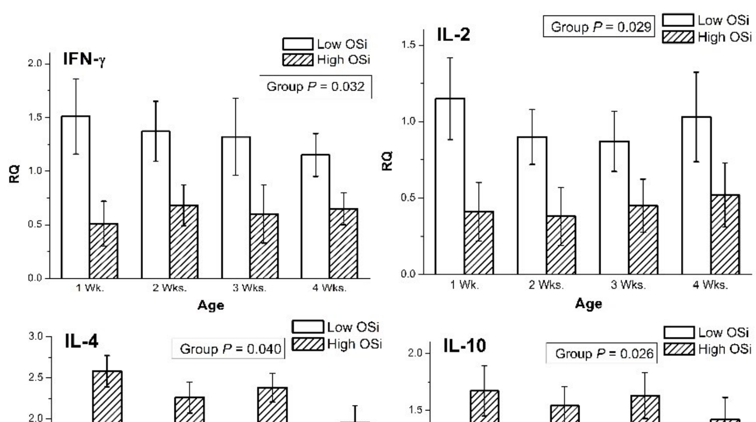

Figure 3. Relative gene expression of Th1 (IFN-γ and IL-2) and Th2 (IL-4 and IL-10) cytokines in PBMCs of newborn calves according to the calves' oxidant status. (Low OSi = Lower degree of oxidant status; RQ = Relative Quantity)

These findings indicate that calves exposed to higher OS have an increased Th2 and reduced Th1 response in comparison to the calves exposed to a lower degree of OS. Although these data do not prove a causative role of OS in shifting the differentiation of T helper cells (↑ Th2, ↓ Th1), previous studies have demonstrated that OS promotes a polarization of human T cell differentiation toward the Th2 phenotype (King et al., 2006;

Kasic et al., 2011). Th2 responses are characterized by a reduced immune memory capacity that impacts the effectiveness of the immune response of newborn calves following immunization (Chase et al., 2008). Hence, it is critical to determine how OS alters key lymphocyte functions relevant for vaccine effectiveness and the extent to which these functions can be rescued with adequate antioxidant micronutrient supplementation.

Preventive measures and future research

As for periparturient cattle, several strategies exist to decrease the risk of OS in neonatal calves. Below, some of the most common ones are summarized, identifying some of the gaps in knowledge that are still present:

Maternal Supplementation with Antioxidants

Supplementation of antioxidants during the dry period slightly above NRC (2001) requirements has shown beneficial effects for cow health and productivity (Abuelo et al., 2015). However, given the carry-over effect of maternal OS on neonatal metabolic and immune function, this practice can also have beneficial effects in the offspring. However, research proving the effects of maternal antioxidant supplementation on calf morbidity and mortality rates is, to the best of the author's knowledge, non-existing to date.

In humans, antenatal supplementation of antioxidant vitamins and minerals has long been a recommended practice to reduce OS at delivery (Bolisetty et al., 2002; Scaife et al., 2006). Some studies in cattle have also shown that dry-period antioxidant supplementation enhances the antioxidative profile of newborn calves (Abdelrahman and Kincaid, 1995; Horn et al., 2010; Jacometo et al., 2015). Nevertheless, various factor limit this route in cattle: (1) the epitheliochorial nature of the ruminants' placenta limits the types of antioxidants that can be transmitted transplacentally, (2) dry dairy cattle are usually already supplemented with considerable amounts of some antioxidants (e.g., selenium close to the US legal limit of 0.3 ppm) for the prevention of transition diseases, (3) excessive antioxidant supplementation can have downstream effects in the health of dairy cattle (Bouwstra et al., 2010a; Bouwstra et al., 2010b; Abuelo et al., 2015) and has been linked with stillbirths in humans (Joshi et al., 2008). Hence, dry cows should not receive antioxidants in amounts significantly exceeding the NRC (2001) requirements.

Colostrum: A Source of Antioxidants and Pro-Oxidants

The importance of colostrum ingestion to the health of the neonatal calf has been well-known for several decades (Besser and Gay, 1994). However, this has been primarily attributed to the acquisition of passive immunity (immunoglobulins) to infectious diseases with calves experiencing failure of passive transfer showing decreased survival rates on farms compared to those with adequate blood immunoglobulin concentrations (Godden, 2008). In addition to immunoglobulins, colostrum is also rich in other beneficial substances such as immune cells, growth factors, cytokines, etc. (Stelwagen et al., 2009). Given that colostrum is the first meal that a calf should receive shortly after birth, its antioxidant content is important to offset the birth-associated OS. However, compared to normal milk, colostrum has the same amount of oxidants but less antioxidants, with the concentration of the latter increasing progressively from the first milked colostrum onwards (Kankofer and Lipko-Przybylska, 2008; Albera and Kankofer, 2011). Hence, colostrum provides antioxidants to calves but is also a source of pro-oxidants. Nevertheless, newborn calves seem to be able to counter effectively the birth-associated OS (Gaal et al., 2006), with calves showing a gradual decrease in oxidant status biomarkers (Inanami et al., 1999; Albera and Kankofer, 2011). Indeed, Abuelo et al. (2014) found that 2h after colostrum ingestion, calves showed the lowest OSi values of the first months of life. To the best of our knowledge, however, no study has hitherto compared the redox balance between calves that ingest colostrum shortly after birth with those experiencing delayed colostrum ingestion. Hence, it remains unexplored whether this gradual decline in OS following birth is due to the transfer of antioxidants via colostrum, the activation of antioxidative pathways in the calves, or a combination of both.

In addition, colostrum redox balance seems to play a role in immunoglobulin absorption. Selenium supplementation of colostrum increases immunoglobulin absorption (Kamada et al., 2007), and the colostrum redox profile was significantly associated with calves' serum immunoglobulin concentrations (Abuelo et al., 2014). However, none of these studies demonstrated which mechanisms might be implicated and therefore further research is needed. Also, a negative association between colostrum immunoglobulin content and antioxidant capacity has been reported (Abuelo et al., 2014). The authors attributed this finding to a consumption of antioxidants in protecting from peroxidation the highly susceptible immunoglobulins during the colostrogenesis process. Therefore, supplementation of colostrum with antioxidants seems to have additional benefits to the calf beyond counteracting the birth-associated OS. Also, there is now a plethora of research indicating the long-term impact of early-life events and management in the calves' productive life once they reach maturity (Kertz et al., 2017). Hence, studies investigating the long-term implications of supplementation of colostrum with antioxidants in the animals' health and productivity are also required.

Supplementation of Calves with Antioxidants

Other ways of increasing the antioxidant potential of calves are the parenteral or dietary administration of vitamins and trace elements. This is a routine management practice in many farms within the first days of life. It's been well-stablished that vitamin supplementation of dairy calves can increase their performance, metabolism, and immune system (Reddy et al., 1985; Reddy et al., 1986; Reddy et al., 1987a; Reddy et al., 1987b). Parenteral trace mineral supplementation (zinc, selenium, manganese, and copper) at 3 and 30 days of life resulted in increased neutrophil function and glutathione peroxidase activity and decreased incidence of health disorders when compared to the control group (Teixeira et al., 2014). Also, trace mineral supplementation concurrent with a polyvalent viral vaccine administration at 30 days of age resulted in improved cell-mediated immune responses (Palomares et al., 2016). However, whether this observed increase improves the vaccine's protection against infection remains unknown.

It is important to note, however, that the NRC (2001) requirements were initially developed to prevent deficiencies and there are no clear guidelines of the levels of antioxidant supplementation for optimized performance. Considering that it is likely that as happens in adult cows, excessive antioxidant supplementation can have detrimental effects on calf health and performance, caution must be exerted when supplementing antioxidants above levels deemed safe by the scientific literature. Indeed, there are reports of toxicosis due to excessive supplementation (MacDonald et al., 1981). This might be even more relevant for those antioxidants, such as selenium, that can be transferred via the placenta when the dams are also supplemented.

Summary

Redox balance is essential for several biological processes of dairy cows and calves. However, when an imbalance exists between the production of pro-oxidants and the animals' antioxidant abilities, OS can develop, and this has been associated with immune and metabolic dysfunction. Also, in pregnant animals, the degree of OS experienced not only puts the dams at risk of subsequent diseases during the onset of lactation, but also have an impact on the offspring. However, antioxidant therapy is capable of protecting against OS-conditions, and several methods for delivery of antioxidants are routinely used in dairy farms. Nevertheless, the findings have been inconsistent at times with some studies not showing an effect. Hence, more research is still needed to provide evidence-based guidance on levels and timing of supplementation that provide an effective improvement of the animals' health status.

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